REMARKS

Objections to the Specification

The Abstract of the Disclosure has been objected to for failing to reflect the invention as being a being a method of using preventatives or remedies. The Abstract of the Disclosure has been replaced with the attached Abstract, which recites that the invention is drawn to a method. No new matter has been added by the new Abstract.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-3 and 5-7 have been rejected under 35 U.S.C. §112, first paragraph for lack of enablement. More specifically, the Examiner asserts that the specification is only enabled for preventing some autoimmune demyelinating diseases using some substances. The Examiner further notes that the specification is enabled for the treatment, but not the prevention of the disease.

Claim 1 has been amended to delete the reference to "preventing." Withdrawal of the rejection is therefore respectfully requested.

Claims 1, 6 and 7 have been rejected under 35 U.S.C. § 112, first paragraph for lack of written description. More specifically, the Examiner asserts that claims 1, 6 and 7 encompass embodiments, which are not adequately described in the specification wherein the target of the apoptosis suppressing substance is not Fas or Fas ligand. The claims have been amended

to incorporate the subject matter of claim 2, which has not been rejected. As such, the rejection is overcome and withdrawal thereof is respectfully requested.

Rejections under 35 U.S.C. §103

The Examiner has made five separate rejections of the invention as being obvious over the prior art, which are individually detailed below. However, all five of the prior art rejections are based on the following premises and/or conclusions by the Examiner.

Premise 1) - It is well-known to use Fas antagonists for treating, rheumatoid arthritis ("RA").

Premise 2) - RA and multiple sclerosis ("MS") are related diseases.

Conclusion - Based on Premise 1 and Premise 2 it would be obvious to use Fas antagonists to treat autoimmune demyelinating diseases.

However, the conclusion reached by the Examiner is incorrect because *Premise 2)*, that RA and MS are related diseases, is both unsupported and incorrect.

The Examiner has provided no evidence that supports the premise that autoimmune demyelinating diseases may be treated using the same methods as RA. According to disease classification, RA and MS are both included in the higher category of "autoimmune diseases." See Attachment A showing the data on disease categories from the MeSH Browser. Applicants

assume that when the Examiner refers to diseases as being "related" he intends that if a therapeutic effect on disease "A" is shown, it would be obvious to treat a "related" disease "B" by the same method. However, as seen on the information contained in the MeSH Browser, "autoimmune diseases" are classified into 21 types of diseases. If the Examiner's conclusion is true and RA and MS are related diseases for purposes of responding to the same therapies, then all 21 diseases listed on the MeSH Browser as autoimmune diseases would be considered "related" in accordance with the standard used by the Examiner. Using the Examiner's reasoning and basis for determining obviousness of the invention, dermatitis herpetiformis, diabetes mellitus and anemia would also be included the "related" diseases and all should respond to the same treatments. However, these diseases clearly do not have common treatment regimes. Thus, the basis used by the Examiner in support of the rejections over the prior art is faulty and as such the invention as claimed is not obvious over the prior art.

Applicants further note the in all of the references relied on by the Examiner for asserting that MS and RA are related, MS is only mentioned in the context of the "Background" sections of the references. None of the references discuss common treatments for MS and RA or teach that a treatment used for RA is suitable for MS.

Each rejection is addressed individually below.

(1) **Keana et al.** - Claims 1-3 and 7 have been rejected under 35 U.S.C. §103 as being obvious over Keana et al. Keana et al. is asserted to teach an apoptosis inhibitor useful in the treatment of multiple sclerosis and the use of the substance as a preventative of Fas ligand-induced apoptosis in mouse liver. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Keana et al. disclose compounds having apoptotic activity. Specifically, Keana et al. disclose compounds for suppressing anti-Fas antibody induced apoptosis in mouse liver. The only disclosure in Keana et al. of MS is in column 3, lines 42-62, which discloses a "wish list"/laundry list of more than 27 diseases ranging from Parkinson's to heart disease and kidney disease to hair loss. There is no disclosure in Keana et al. that any compound having activity against apoptosis is effective against MS and the only demonstrated pharmacological activity is against ischemia. One skilled in the art would not be able to predict from the disclosure of Keana et al. whether administration of a Fas antagonist would be efficacious in treating demyelinating diseases. As such, the present invention is not obvious over Keana et al. and withdrawal of the rejection is respectfully requested.

(2) **Hughes and Crispe in view of Holoshitz et al. and D'Souza et al.** - Claims 1-3, 6 and 7 have been rejected under 35 U.S.C. §103 as being obvious over Hughes and Crispe in view of

Holoshitz et al. and D'Souza et al. Hughes is asserted to teach the use of a soluble variant of Fas to inhibit apoptosis. Hughes is asserted to fail to teach the use of the variant to treat or inhibit autoimmune demyelinating diseases. Holoshitz et al. is asserted to disclose the involvement of the Fas-Fas ligand interaction in demyelinating immune diseases and D'Souza et al. is asserted to teach the involvement of Fas-Fas ligand with multiple sclerosis. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Hughes and Crispe disclose a soluble variant of Fas which blocks Fas ligand-induced apoptosis. The Examiner asserts that Holoshitz et al. disclose in columns 1 and 5 that the Fas-Fas ligand pathway is linked to autoimmune demyelinating diseases, including MS. However, column 2, lines 28-35 of Holoshitz et al. clearly state that the subject matter disclosed therein is drawn to the use of sphinogmyelin signal transduction inhibitors having an "apoptosis **inducing** activity" for treating RA. Column 1, lines 9-20, mention that the invention of Holoshitz et al. is, in fact, drawn to methods of treating autoimmune diseases, in particular RA. However, MS is merely cited in column 1, line 19, in the "Background" section as an example of an autoimmune disease. Thus, if read in its entirety, Holoshitz et al. teaches that sphingomyelin signal transduction inhibitors may be used to treat RA. Holoshitz et al. does not teach that these inhibitors can treat MS and even more importantly, the compounds of Holoshitz et al. are not Fas antagonists. Thus, Holoshitz et al.

does not teach the involvement of the Fas-Fas ligand interaction in autoimmune demyelinating diseases.

D'Souza et al. summarizes that elevated Fas expression was confirmed using oligodendrocytes (OLs) in MS lesions but apoptosis was not observed with an anti-Fas antibody used as a stimulus on the OLs. The final sentence of D'Souza et al. states, "the availability of soluble Fas, neutralizing antibodies to Fas or Fas ligand, or inhibitors of Fas ligand induction or Fas-mediated cell death provides potential means to manipulate this signaling pathway for therapeutic applications in MS." However, this statement clearly reflects a speculation and supposition by the authors of the article. There is no disclosure in D'Souza et al. as to whether these substances actually have any effect for the treatment of MS. D'Souza et al. demonstrate only that apoptosis is <u>not</u> seen when OLs are stimulated with anti-Fas antibodies. Thus, D'Souza et al. actually teaches away from an involvement of Fas-Fas ligand in MS. One skilled in the art would conclude from D'Souza et al. that a Fas antagonist would not likely have efficacy in treating MS because of the lack of effect on OLs by anti-Fas antibodies. Thus, D'Souza et al. and Holoshitz et al. fail to compensate for the deficiencies of Hughes and Crispe and the present invention is not achieved by the combined references. Withdrawal of the rejection is respectfully requested.

(3) **Nagata et al. combined with Holoshitz et al. and Queen et al.** - Claims 1-3 and 5-7 have been rejected as being obvious over Nagata et al. combined with Holoshitz et al. and Queen et al. Nagata et al. is asserted to teach a method of treating autoimmune diseases such as rheumatism, SLE and AIDS by administering anti-Fas ligand antibodies. Holoshitz et al. and Queen et al. are asserted to teach that rheumatoid arthritis and multiple sclerosis are related and may be treated with the same methods. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As discussed above, Holoshitz et al. fails to disclose any compound that may be used to treat MS. Queen et al. disclose Fas ligand fusion proteins; however MS is only disclosed in column 2, "Background", and there is no disclosure as to whether any of the substances having apoptosis inhibitory activity are actually effective in treating MS. In addition, as discussed above, the Examiner bases the rejection on the incorrect premise that RA and MS are related and treatable by similar methods. However, nowhere do either the references or the data from the MeSH browser support this position. As such, the invention is not achieved by combining Nagata et al. with Holoshitz et al. and Queen et al. and withdrawal of the rejection is respectfully requested.

(4) **Lynch et al., in view of D'Souza et al.** - Claims 1-3, 5 and 6 have been rejected under 35 U.S.C. §103 as being

unpatentable over Lynch et al., in view of D'Souza et al. Lynch et al. is asserted to use of anti-Fas receptor antibodies that inhibit the binding of Fas ligands and, thus, inhibit apoptosis. Lynch et al. is further asserted to teach the use of the antibodies to treat rheumatoid arthritis. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As discussed above, D'Souza et al. teaches away from the present invention with results that suggest that the Fas-Fas ligand pathway is not involved with MS. Lynch et al. disclose in column 16, lines 3-14, that anti-Fas antibodies are applicable to SLE, RA and idiopathic CD4+ T lymphocytopenia and HIV infection. However, Lynch et al. is silent regarding MS and does not disclose that MS is included with autoimmune demyelinating diseases. As such, the invention is not achieved when D'Souza et al. and Lynch et al. are combined and withdrawal of the rejection is respectfully requested.

(5) **Lynch et al. in view of Aoyagi et al.** - Claims 1-3 and 5-7 have been rejected under 35 U.S.C. §103 as being obvious over Lynch et al. in view of Aoyagi et al. Further to the teachings of Lynch et al. discussed above, Aoyagi et al. is asserted to teach that treatments for autoimmune diseases can also be used autoimmune demyelinating diseases and that there is little difference between autoimmune diseases generally and autoimmunedemyelinating diseases. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As noted above, Lynch et al. is silent regarding MS and does not disclose that MS is included with autoimmunedemyelinating diseases. Aoyagi et al. is asserted to teach that therapeutic agents for autoimmune diseases can also be used to treat autoimmune demyelinating diseases because the patent refers to anti-Fas antibodies and RA and the Examiner concludes that autoimmune demyelinating diseases are related to RA and can be treated similarly. However, as discussed above, this basic premise of the Examiner is both unsupported and incorrect. Aoyagi et al. teaches on page 2, lines 1-2 that MS is an autoimmune demyelinating disease that belongs to the higher classification of "autoimmune diseases." However, nowhere does Aoyagi et al. disclose that RA and MS are "related." In addition, Aoyagi et al. disclose compounds that are effective in an experimental allergic encephalomyelitis (EAE) model. The compounds of Aoyagi et al. are irrelevant to Fas-Fas ligand interactions. As such, the rejection is based on an unsupported and incorrect premise and the invention is not obvious over the references. Withdrawal of the rejection is respectfully requested.

As the above amendments and remarks address and overcome the objections and rejections to the specification and claims, withdrawal of the objections and rejections and issuance of the Notice of Allowability are respectfully requested.

Should the Examiner have any questions regarding the present application, he is requested to please contact MaryAnne

Armstrong, PhD (Reg. No. 40,069), in the Washington DC area, at (703) 205-8000.

A marked-up version of the amended paragraphs of the specification and claims showing all changes is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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1110-0280P

Attachments: Marked-up version

MARKED-UP VERSION

IN THE ABSTRACT

The Abstract of the Disclosure has been amended to replace the Abstract of the Disclosure with the attached replacement Abstract.

IN THE CLAIMS:

Claim 2 has been cancelled without prejudice or disclaimer of the subject matter contained therein.

Claims 1 and 3-5 have been amended as follows.

1. (Twice Amended) A method for treating ~~and preventing~~ autoimmune demyelinating diseases which comprises administering to a patient in need thereof an effective amount of **a Fas antagonist** ~~an apoptosis-suppressing substance~~.

3. (Twice Amended) The method according to claim **1** ~~2~~ wherein said **Fas antagonist** ~~an apoptosis-suppressing substance~~ is a substance which suppresses Fas-Fas ligand binding.

4. (Thrice Amended) The method according to claim 1 wherein said **Fas antagonist** ~~an apoptosis-suppressing substance~~ is a polypeptide of (a) or (b) as follows:

(a) a polypeptide which comprises an amino acid sequence of a Fas protein that has been arbitrarily mutated at one or more

amino acid residues by substitution, deletion and/or addition, and which has an activity of inhibiting Fas-mediated apoptosis; or

(b) a fusion polypeptide comprising (a) and another polypeptide except (a).

5. (Thrice Amended) The method according to claim 1 wherein said **Fas antagonist** ~~an apoptosis-suppressing substance~~ is an anti-Fas ligand antibody.

Attachment A

NCBI MeSH Browser

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books

Search for [ ] Go Clear

Autoimmune Diseases[Detailed display]

About Entrez

Text Version

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy

PubMed Services
Journal Browser
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
Cubby

Related Resources
Order Documents
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Privacy Policy

Disorders that are characterized by the production of antibodies that react with host tissues or immune effector cells that are autoreactive to endogenous peptides.

Add this term to the Search using operator: AND

All MeSH Categories
- Diseases Category
  - Immunologic Diseases
    - Autoimmune Diseases
      - Addison's Disease
      - Anemia, Hemolytic, Autoimmune
      - Anti-Glomerular Basement Membrane Disease
      - Antiphospholipid Syndrome
      - Arthritis, Rheumatoid
        - Arthritis, Juvenile Rheumatoid
        - Felty's Syndrome
        - Sjogren's Syndrome
        - Spondylitis, Ankylosing
        - Still's Disease, Adult-Onset
      - Autoimmune Diseases of the Nervous System
        - Demyelinating Autoimmune Diseases, CNS +
        - Disease Models, Autoimmune, Nervous System +
        - Lambert-Eaton Myasthenic Syndrome
        - Leukoencephalitis, Acute Hemorrhagic
        - Myasthenia Gravis +
        - Polyradiculoneuropathy +
        - Stiff-Person Syndrome
        - Uveomeningoencephalitic Syndrome
        - Vasculitis, Central Nervous System +
      - Dermatitis Herpetiformis
      - Diabetes Mellitus, Insulin-Dependent
      - Glomerulonephritis, IGA
      - Glomerulonephritis, Membranous
      - Goodpasture Syndrome
      - Graves' Disease
      - Lambert-Eaton Myasthenic Syndrome
      - Lupus Erythematosus, Systemic
        - Lupus Nephritis
        - Lupus Vasculitis, Central Nervous System
      - Ophthalmia, Sympathetic

Pemphigoid, Bullous
Pemphigus
Pemphigus, Benign Familial
Polyendocrinopathies, Autoimmune
Purpura, Thrombocytopenic, Idiopathic
Reiter Disease
Thyroiditis, Autoimmune